REMARKS

In view of the above amendments and the following remarks, the Examiner is requested to allow claims 1-35, 67-101 and 144-149, the only claims pending and under examination in this application.

Claim Rejections – 35 U.S.C. § 103(a)

Claims 1-34, 67-76, 78-100, and 148-149 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Baldarelli et al. (U.S. Patent No. 6,015,714) in view of Brockhurst (U.S. Published Application No. 2003/0104376). This rejection is respectfully traversed.

In making this rejection, the Examiner asserts Baldarelli et al. teach all of the limitations of the claims but for using modified A, T, G or C or a nucleic acid which is enzymatically produced using a circular template. For these missing elements, the Examiner looks to Brockhurst, asserting that it would be obvious to incorporate these elements of Brockhurst into the method of ca

As developed below, it is respectfully submitted that one would not in fact be motivated to modify Baldarelli et al. with these specific elements of Brockhurst.

Baldarelli et al. is silent with respect to the improvement in sequencing achieved by generating nucleic acid polymers having repeats. A reading of Baldarelli et al. would not provide the reader with any reason to use repeats. The primary emphasis of Baldarelli et al. is the method of sequencing, a method that does not involve chemical or enzymatic reactions. Baldarelli et al. notes that his method is faster and can sequence longer nucleic acid polymers, but he is comparing his method with prior chemical and enzymatic methods. Baldarelli et al. devotes little disclosure to the structure of the nucleic acid polymer that is to be sequenced, and there is nothing in Baldarelli et al. regarding the influence of the structure of the polymer on the rate of sequencing. Examples 7 and 8 of Baldarelli et al. relate only to the feasibility of sequencing two different oligonucleotide homopolymers and an oligonucleotide heteropolymer, respectively, and not to the effect of the polymers on the rate of sequencing.

Brockhurst is not directed to a sequencing method at all, but instead is directed to a rapid and efficient assay to identify naturally occurring nucleotide repeat regions of interest. The invention of Brockhurst is summarized by Brockhurst as follows:

> [0012] Another aspect of the present invention provides a method of identifying or otherwise detecting a nucleotide repeat region characterized by a particular length in a nucleic acid molecule, said method comprising annealing to a single stranded template form said nucleic acid molecule at least two flanking oligonucleotides which flank the putative nucleotide repeat region to be identified and, in a multiplicity of separate reactions, a spacer oligonucleotide of a defined length in each separate reaction which spacer oligonucleotide anneals to all or part of the nucleotide sequence between said flanking oligonucleotides wherein one of said flanking oligonucleotides is labelled with a capturable moiety and the other of said flanking oligonucleotide is labelled with a detectable moiety and subjecting said annealed molecules to ligation reactions and attachment conditions such that the oligonucleotide comprising a terminal capturable moiety anchors the annealed, potentially ligated nucleic acid molecule to a solid support; subjecting said anchored nucleic acid molecule to denaturing means such that the template nucleic strand of the nucleic acid molecule separates from the annealed oligonucleotides and then screening for said detectable moiety on a flanking oligonucleotide wherein the presence of a detectable signal is indicative that the three oligonucleotides are in tandem ligatable arrangement wherein the spacer oligonucleotide in the reaction giving the signal corresponds to the length of the nucleotide repeat region.

By hybridizing terminal sequences having, respectively, a capturable moiety and a detectable moiety and a third nucleic acid that hybridizes to the repeat region of interest, and then subjecting the product to ligation conditions, if the repeat region of interest is present, it can be readily detected. Brockhurst can provide this ready detection of the sequence without having to actually sequence the target nucleic acid of interest. As such, Brockhurst has nothing to do with sequencing.

In the method disclosed by Brockhurst, it is mentioned that one could amplify the target nucleic acid prior to detection, and several different ways of amplification are disclosed in paragraph 39, which reads:

> [0039] Although the present invention may be practised directly on single stranded template from a non-amplified nucleic acid molecule, in a preferred embodiment the template nucleic acid molecule is from a nucleic acid molecule which has been subjected to amplification. Any of a range of amplification reactions may be employed including PCR, rolling circle amplification and Qβ replicase based amplification amongst others.

Thus rolling circle is only one way that amplification is suggested, and the other methods of amplification would not result in a repeat molecule.

It is respectfully submitted that one of skill in the art would not be motivated in any way to modify the Baldarelli method with anything taught in Brockhurst as suggested by the Examiner.

'In order to rely on a reference as a basis for rejection of an applicant's invention, the reference must either be in the field of applicant's endeavor or, if not, then be reasonably pertinent to the particular problem with which the inventor was concerned.' *In re Oetiker*, 977 F.2d 1443, 1446, 24 USPQ2d 1443, 1445 (Fed. Cir. 1992). See also *In re Deminski*, 796 F.2d 436, 230 USPQ 313 (Fed. Cir. 1986); *In re Clay*, 966 F.2d 656, 659, 23 USPQ2d 1058, 1060-61 (Fed. Cir. 1992) ('A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem.'); *Wang Laboratories Inc. v. Toshiba Corp.*, 993 F.2d 858, 26 USPQ2d 1767 (Fed. Cir. 1993); and *State Contracting & Eng'g Corp. v. Condotte America, Inc.*, 346 F.3d 1057, 1069, 68 USPQ2d 1481, 1490 (Fed. Cir. 2003) (where the general scope of a reference is outside the pertinent field of endeavor, the reference may be considered analogous art if subject matter disclosed therein is relevant to the particular problem with which the inventor is involved).

One would not be so motivated to combine Baldarelli with Brockhurst because the two disclosures are directed to completely different protocols. While Baldarelli is directed to sequencing, Brockhurst is directed to a method that has nothing to do with sequencing. Brockhurst is directed to a hybridization based assay, which is not in the same field of endeavor as sequencing or reasonably pertinent to sequencing using a nanopore. As such, one of skill in the art looking to improve any problems with Baldarelli would not look to Brockhurst for any guidance, since Brockhurst has nothing to do with sequencing.

Furthermore, when Brockhurst discloses amplification, it is merely to make more copies of the target nucleic acid available for detection by the non-sequencing method of Brockhurst. While the method by Brockhurst may benefit from such amplification because it is a hybridization based assay, there is no teaching or suggestion in either Brockhurst or Baldarelli that such amplification would have any benefit at all in a sequencing method as disclosed in Baldarelli, where the individual nucleotides are detected one at a time. One of skill in the art would not be motivated to choose any of the amplification methods disclosed by Baldarelli, much less the rolling circle protocol which is disclosed as one of many possible amplification protocols.

It is well-settled decisional law that the fact that the invention of a primary prior art reference *could* be modified to form the claimed invention would not have made the modification obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 733 F.2d 900, 221 USPQ 1125 (Fed. Cir. 1984); *In re Laskowski*, 871 F.2d 115, 10 USPQ2d 1397 (Fed. Cir. 1989). In *Environmental Instruments, Inc. v. Sutron Corp.*, 877 F.2d 1561, 11 USPQ2d 1132 (Fed. Cir. 1989), the court affirmed a combination of documents because the secondary reference plainly suggested the replacement of an aspect of the primary reference in order to arrive at the claimed invention. Therefore, the mere disclosure in a secondary document of the elements needed to arrive at Applicant's invention by modification of a primary document is insufficient to establish *prima facie* obviousness. Without a plain suggestion *in the cited art* to make such a modification, the modification exists only in Applicant's own disclosure, which is contrary to the case law and to MPEP

§ 2143. A rejection such as the present rejection, which is based only on the presence of the requisite elements in a secondary document, is evidence of quintessential hindsight, and not of *prima facie* obviousness. The two cited documents are sufficiently diverse so as not to suggest plainly the modification put forth by the Examiner.

No reason can be found in either Baldarelli or Brockhurst as to why one would choose an amplified nucleic acid to sequence in Baldarelli, much less one that has been produced from a circular template, since the sequencing method of Baldarelli relies on detection of individual nucleotides and is not a hybridization based assay.

Only Applicant's disclosure provides a reason to use repeats. Moreover, unless one were using (improperly) Applicant's disclosure as a guide, there would have been no reason to select the rolling circle method from among the many different methods disclosed in paragraph 0039 of Brockhurst, as well as the many known in the art for amplification.

Significantly, neither Baldarelli et al. nor Brockhurst teaches or suggests that using modified nucleotides reduces secondary structure that in turn increases the rate of nanopore sequencing, as in Applicant's invention. Applicant was the first to recognize the specific problem of the effect of secondary structure on the rate of nanopore sequencing, and then succeeded in solving that problem.

Recognition by Appellants of a problem in the art and solving that problem are themselves a basis for a determination of the unobviousness of Appellants' claimed invention:

"[Where] there is no evidence of record that a person of ordinary skill in the art at the time of [an applicant's] invention would have expected [a problem] ... to exist at all, it is not proper to conclude that [an invention] ... which solves this problem ... would have been obvious to that hypothetical person of ordinary skill in the art." *In re Peehs*, 612 F.2d 1287, 1290, 204 USPQ 835 (CCPA 1980) (citing *In re Nomiya*, 509 F.2d 566, 572, 184 USPQ 607, 612-13 (CCPA 1975))(emphasis added).

Accordingly, for at least the reason that there would have been no motivation to combine the cited documents, much less to combine them in the manner suggested by the Examiner, there is no *prima facie* obviousness. Withdrawal of this rejection is respectfully requested.

Claims 34, 77 and 144-147 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Baldarelli in view of Brockhurst and further in view of Dellinger. As reviewed above, Baldarelli in view of Brockhurst is fundamentally deficient in failing to teach or suggest a method of sequencing a nucleic acid generated from a circular template. As Dellinger was cited solely for the specific modified bases appearing in these claims, it fails to make up the fundamental deficiency. As such, this rejection may be withdrawn.

Claims 35 and 101 are rejected under Baldarelli in view of Brockhurst, and further in view of Thorp et al. As reviewed above, Baldarelli in view of Brockhurst is fundamentally deficient in failing to teach or suggest a method of sequencing a nucleic acid generated from a circular template. Thorp et al. was cited for its alleged teaching of a method of detecting a nucleic acid by using electron tunneling. Accordingly, Thorp et al. does nothing to remedy the deficiencies put forth *supra* of the combination of Baldarelli et al. and Brockhurst. As such, withdrawal of this rejection is respectfully requested.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone Bret Field at (650) 833-7770.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10001492-2.

Respectfully submitted,

Date: April 30, 2007

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